

LETTER TO THE EDITOR

Safety of BNT162b2 mRNA COVID-19 Vaccine Batches: A Nationwide Cohort Study

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Received: 9 September 2025 | **Accepted:** 24 October 2025

Funding: The authors' work in this area of research has been supported by donation-based crowdfunding (Danish Ministry of Justice, Department of Civil Affairs, journal number 23-700-06725). The funding source did not have any role in the writing of the manuscript or the decision to submit it for publication.

We read with interest the study of Hviid and Svalgaard which purports to provide reassurance concerning the safety of the BNT162b2 vaccine across different batches used in Denmark [1]. The results appear to contradict our previous report of a batch-dependent safety signal for the vaccine in Denmark, and since the authors cite that limitations were suggested to our results, they might also have cited our published response to these concerns [2, 3]. Moreover, it is notable that the batch-dependent safety signal for the BNT162b2 vaccine in Denmark was subsequently reproduced in Sweden and the Czech Republic, and that all these studies examined reported adverse events, not discharge diagnoses from hospitals as was done by Hviid and Svalgaard [4, 5]. Indeed, the first Periodic Safety Update Report (PSUR) for the BNT162b2 vaccine that was submitted to the European Medicines Agency by the market authorization holder (BioNTech) on 19 August 2021 also disclosed considerable variation in the numbers of suspected adverse events between different BNT162b2 batches administered during the early vaccination campaign [6]. In their study, the authors from Statens Serum Institut, which distributes COVID-19 vaccines in Denmark, compared 28-day outcomes for three groups of Danes vaccinated with BNT162b2 vaccines from either of three consecutive vaccine batch clusters (used consecutively and almost exclusively in 2021 and 2022) for which we found substantial differences in the rates of reported adverse events [2, 3]. Subjects were matched on age (10-year intervals), sex, and vaccination priority group, and no safety differences were observed between subjects vaccinated with vaccines from either three batch clusters, apart from slightly increased rates of arrhythmias in group 3 vs. groups 1 and 2 [1]. However, all-cause mortality (ACM) was

significantly lower in the group 3 vs. group 1 (HR 0.81 [95% CI, 0.71–0.93]) comparison, and higher in the group 3 vs. group 2 (HR 1.09 [1.01–1.17]) comparison, respectively. This apparent batch-dependent ACM signal was not further commented upon by the authors, but it seems remarkable, not least in view of the absence of substantial differences in the other safety outcomes of the three groups that were supposedly adequately matched. To further explore this apparent inconsistency, we used publicly available 2021 and 2022 Danish population data on age, sex and ACM and calculated 28-day average age-adjusted ACMs for subjects in the three respective matched groups [7]. Intriguingly, these results indicate that the ACM captured in the authors' comparison of group 3 vs. group 1 comprised only 87.3% (2021) to 89.7% (2022) of the age-matched mean ACM in Denmark, while the ACM captured in the group 3 vs. group 1 comparison comprised 126.6% (2021) to 128.5% (2022) of the average age-matched ACM. This apparent divergence of approximately 40% with under-capture as well as over-capture of age-adjusted ACMs in the two comparisons of age-matched groups (where group 3 data was included in both comparisons), would appear to question the validity of the matching procedure and therefore casts doubt on the conclusions of the study [1]. Accordingly, although Hviid and Svalgaard suggest that their study circumvented many of the weaknesses of our report, the matching procedure used in their study might have introduced an important new source of bias. We encourage the authors to disclose summary 28-day ACM data for all age, sex, and vaccine priority groups for every combination of comparisons between the three batch cluster groups, so that readers can ascertain the soundness of the matching procedure, that is, whether under- and

over-capture of ACM was symmetrically distributed in all these combinations.

Conflicts of Interest

The authors declare no conflicts of interest.

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